

a degree of substitution of 0.65-0.90.

Applicants have amended claims 17 and 31 to specify that the preferred binding agent, carboxymethylcellulose, is of low viscosity grade having a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90. Support for this amendment is found in the application at p. 45, line 21 to p. 46, line 14.

None of the amendments add new matter.

Applicants address the Examiner's rejection below:

35 U.S.C. § 102(b): Claims 1, 7-9, 11-14 and 20-24

The Examiner has maintained the rejection of claims 1, 7-9, 11-14 and 20-24 under 35 U.S.C. § 102(b) as being anticipated by WO 94/15653 ("Ammann"). The Examiner states that Ammann teaches that the polymer may be CMC or collagen or a combination thereof.

Applicants have amended claims 1, 20 and 23 to recite that the claimed device must include a low viscosity binding agent having a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90. Support for this amendment is provided on p. 45, line 21 to p. 46, line 45. Specifically, the application at p. 46, lines 6-14 recites:

Contrary to teachings in the art, it has now been discovered that high viscosity CMC adversely affects bone formation when used in an improved osteogenic device comprising a matrix as defined herein...Unexpectedly, when a biological material such as collagen is used as a matrix, the improved device must be formulated with low viscosity CMC (approximately 10-50 cP, or 50-200 cP) in order to induce bone and/or cartilage formation, as taught herein.

Thus, applicants have disclosed that the viscosity of the carboxymethylcellulose ("CMC") used to formulate an osteogenic device is critical for bone formation. When a synthetic polymer matrix is used, high viscosity CMC can be used to induce bone formation. However, when a material as defined in claim 1 (i.e., not a synthetic polymer or demineralized bone) is used as a matrix (e.g., collagen), the osteogenic device must be formulated with low viscosity CMC (approximately 10-50 cP, or 50-200 cP) in order to induce bone and/or cartilage formation. This is an unexpected result and would not have been known by one of ordinary skill in the art.

Ammann does not teach the critical feature of a low viscosity binding agent as claimed in the present application. Ammann teaches compositions of TGF- β and TCP useful for bone formation. Furthermore, Ammann teaches that the compositions may also contain an

effective amount of a polymer for enhancing the consistency of the formulation and provides at best a general suggestion of combining numerous carbohydrates and/or insoluble proteins including CMC or collagen or a combination of these. Ammann does not teach the critical combination of collagen and low-viscosity CMC as recited in claims 1, 7-9, 11-14 and 20-24.

Accordingly, applicants request that the Examiner withdraw this novelty rejection.

35 U.S.C. § 102(b): Claims 20 and 22

The Examiner has maintained the rejection of claims 20 and 22 under 35 U.S.C. § 102(b) as being anticipated by Beck et al., J. Bone and Min. Res. 6:1257-65, 1991 ("Beck"). Specifically, the Examiner contends that there is no teaching in the specification that would exclude TGF- β from being an osteogenic protein and that TGF- β is an osteogenic protein as is manifestly obvious from the teachings of Beck. Applicants traverse.

Applicants respectfully submit that osteogenic proteins are defined in the specification on p. 2, lines 15-23:

Thus, true osteogenic proteins are capable of inducing the above-described cascade of morphogenic events resulting in endochondral bone formation...these

osteogenic factors...can induce recruitment of accessible progenitor cells and stimulate their proliferation, thereby inducing differentiation into chondrocytes and osteoblasts, and further inducing differentiation of intermediate cartilage, vascularization, bone formation, remodeling, and finally, marrow differentiation.

The formation of a cartilagenous intermediate is a crucial step in the cascade of events that lead to formation of endochondral bone.

In contrast, Beck states on p. 1262 that:

a single application of TGF- β 1 to a skull defect is sufficient to induce the cascade of events that result in bone formation. However, although bone formation continues until complete closure occurs, this occurs without evidence of cartilagenous intermediate. In contrast, BMPs admixed with demineralized bone powders and implanted at soft tissue sites or sites of bony defects induce bone with a cartilagenous intermediate.

According to Beck, TGF- β does not induce intermediate cartilage formation which is a necessary step in the cascade of morphogenic events resulting in endochondral bone formation as defined for osteogenic proteins in the application.

Furthermore, applicants submit a prefilings reference, Sampath³, that demonstrates that TGF- β is a growth factor and does not lead to cartilage formation, a crucial step in endochondral bone formation (see p. 7111-7112).

For all the above reasons, applicants request that the Examiner withdraw this novelty rejection.

35 U.S.C. § 102(e): Claims 1-5, 7-9, 11-13 and 31

The Examiner has maintained the rejection of claims 1-5, 7-9, 11-13 and 31 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,674,292 ("Tucker"). The Examiner asserts that Tucker has a common inventor with the instant application and based upon the earlier effective U.S. filing date of the reference constitutes prior art under 35 U.S.C. § 102(e). Applicants traverse.

As discussed above, applicants have amended claims 1-5, 7-9, 11-13 and 31 to recite that the device comprises a low viscosity binding agent with a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90.

³ Sampath, T. K. et al., "Isolation of osteogenin, an extracellular matrix-associated, bone-inductive protein, by heparin affinity chromatography," PNAS 84, pp. 7109-7113 (1987) (Exhibit C).

Tucker teaches terminally sterilized osteogenic devices containing a composition comprising an osteogenic protein and a carrier, which are capable of inducing bone formation following implantation into a mammal. Tucker, however, does not recite the critical combination of collagen and low viscosity CMC in the composition as recited in claims 1-5, 7-9, 11-13 and 31. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 103(a)

Claims 1-5 and 31: Ammann in view of Kuberasampath

The Examiner has maintained the rejection of claims 1-5 and 31 under 35 U.S.C. § 103(a) as being obvious over Ammann and U.S. Patent 5,645,591 ("Kuberasampath"). The Examiner asserts that Ammann teaches that the polymer may be CMC or collagen or a combination of these and that it would have been obvious to make an osteogenic device comprising TGF- β as taught by Ammann and modify that teaching by making an osteogenic device comprising OP-1, as taught by Kuberasampath, with a reasonable expectation of success. Applicants traverse.

Ammann teaches compositions of TGF- β and TCP

useful for bone formation that may also contain an effective amount of a polymer for enhancing the consistency of the formulation. Kuberasampath teaches a synthetic bone matrix in an osteogenic device including an osteogenic protein and a porous matrix comprising a polymer of cross-linked collagen and glycosaminoglycan.

As described above, amended claims 1-5 and 31 recite a device for inducing local bone or cartilage formation using a low viscosity binding agent having a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90. This characteristic of the binding agent exhibits unexpected results in bone formation when used in an osteogenic device in combination with a matrix as claimed in the present application. Neither Ammann nor Kuberasampath, either alone or in combination, teaches this feature.

Furthermore, Kuberasampath discloses using a synthetic collagen-GAG polymer as a matrix material. Kuberasampath's device contains a collagen-GAG synthetic polymer made artificially by cross-linking collagen and GAG (see p. 8). Kuberasampath does not teach or even suggest the use of any matrix material other than a synthetic polymer of collagen-GAG, much less the use of a matrix material that is not a synthetic polymer.

Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

Claims 1, 6, 15, 16, 32, 33, 35 and 36: Ammann in view of Ogawa

The Examiner has maintained the rejection of claims 1, 6, 15, 16, 32, 33, 35 and 36 under 35 U.S.C. § 103(a) as being obvious over Ammann and Ogawa et al., J. Biol. Chem. 267: 14233-7, 1992 ("Ogawa"). The Examiner states that Ammann teaches that the polymer may be CMC or collagen or a combination thereof. Furthermore, the Examiner asserts that there is no teaching in the specification that would exclude TGF- β from being an osteogenic protein. Applicants traverse.

Amended claims 1, 6, 15, 16, 32, 33, 35 and 36 recite a device or kit wherein the binding agent has a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90.

As discussed above, Ammann teaches compositions of TGF- β and TCP useful for bone formation that may further contain an effective amount of a polymer for enhancing the consistency of the formulation. Ogawa teaches a composition of TGF- β and BMP and the use of saline as wetting agent in an osteogenic device. Neither Ammann nor Ogawa, either alone or in combination, teaches

a composition comprising collagen and a low viscosity binding agent as recited in amended claims 1, 6, 15, 16, 32, 33, 35 and 36. Accordingly, applicants, request that the Examiner withdraw this rejection.

Claims 17-19 and 25: Ammann and Cook in view of Ogawa

The Examiner has maintained the rejection of claims 17-19 and 25 under 35 U.S.C. § 103(a) as being obvious over Ammann and Cook et al., Clin. Ortho. Rel. Res. 301: 302-312, 1994 ("Cook") in view of Ogawa. The Examiner asserts that it would have been obvious to one skilled in the art at the time of the invention to make an osteogenic device comprising TGF- β 1, collagen and CMC, as taught by Ammann and to modify that teaching by using 2.5 mg of OP-1/500 mg of collagen, as taught by Cook, and to further modify that teaching by wetting the device with saline, as taught by Ogawa with a reasonable expectation of success. Applicants traverse.

Amended claims 17-19 and 25 recite a device comprising CMC having a viscosity of about 10-200 cP or a degree of substitution of 0.65-0.90. As discussed above, Ammann does not teach or even suggest the feature of low-viscosity carboxymethylcellulose, as required in amended claims 17-19 and 25. Cook teaches the use of OP-1 in a

bovine bone collagen carrier to induce bone formation in a segmental defect model. Ogawa teaches a composition of TGF- β and BMP and the use of saline as wetting agent in an osteogenic device.

Thus, nothing in Ammann, Cook or Ogawa, either alone or in combination, teaches a low viscosity carboxymethylcellulose as recited in amended claims 17-19 and 25. One of ordinary skill in the art would not have arrived at the claimed invention by combining the three cited references. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

Respectfully submitted,



James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorneys for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York 10020
Tel.: (212) 596-9000